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Process for the preparation of nicotinaldehydes

The invention relates to a process for the preparation of nicotinaldehydes by reduction of the corresponding nicotinic acid morpholinamides.

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Nicotinaldehydes are important intermediates or end products in industrial organic chemistry. Appropriately substituted derivatives, such as, for example, arylnicotinaldehydes, are, *inter alia*, valuable intermediates for the synthesis of highly value-added end products or are themselves such end products, in particular for crop protection, such as, for example, fungicides, 10 insecticides, herbicides or pesticides, or for the preparation of highly pharmaceutically active substances.

There is therefore interest in an extremely economical process for the production of these compounds on a large industrial scale

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As an unstable oxidation state between alcohol and carboxylic acid, aldehydes are generally accessible with difficulty. Aromatic aldehydes in particular easily oxidise to the corresponding carboxylic acids or disproportionate under alkaline conditions to give alcohol and carboxylic acid. In the 20 reductive preparation of nicotinaldehyde derivatives, reduction to the dihydropyridine occurs as an additional side reaction.

There are preparation methods known from the literature which describe selective reduction of carboxylic acid derivatives as far as the aldehyde stage. These methods generally require cooling of the reaction mixture in 25 order to minimise over-reductions.

Special methods for the reduction of nicotinic acid derivatives are also known. Thus, for example, DE-A 100 05 150 describes a process for the preparation of 5-arylnicotinaldehydes by reduction of the corresponding 5-arylnicotinic acids by means of catalytic hydrogenation.

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H.C. Brown and A.Tsukamoto in J. Am. Chem. Soc. 81 , p. 502 (1959) described the reduction of nicotinamides using triethoxylithium aluminium hydride. However, a low reaction temperature was described as indispensable here, and the yield was below 90% of theory.

5 Further known processes for the preparation of nicotinaldehydes by reduction are shown in the following review.

	No.	Number of reaction steps	Nicotinic acid derivative	Reducing agent	Reaction conditions	Yield	Literature
10	1	2	diethylamide	Cp ₂ Zr(H)Cl	room temp./ 15 min.	99%	J. Am. Chem. Soc. 48 (2000) 11995-11996
	2	3	nitrile	DiBAH (di-isobutyl-aluminium hydride)	toluene -50°C 2.5 hrs	96%	J. Org. Chem. 64,26 (1999) 9658-9667
15	3	3	nitrile	K amyl-(9)-borabicyclo-nonane	THF 25°C	96%	Tetrahedron Letters 30,28 (1989) 3677-3680
	4	3	nitrile	DiBAH	toluene -12°C	70%	J. Med. Chem. 36,8 (1993) 953-966
20	5	2	hydrazide	NaIO ₄	water/NH ₃	70%	J. Am. Chem. Soc. 74 (1952) 5796
	6	3	N-methylanilide	LiAlH ₄	THF 0°C	65%	Angew. Chemie 65 (1953) 525
25	7	3	nitrile	DiBAH	THF 0°C	62%	J. Med. Chem. 35,21 (1992) 3784-3791
	8	3	sulfonylhydrazide	Na ₂ CO ₃	160°C ethylene glycol	61%	J. Am. Chem. Soc. 80 (1958) 862
30	9	3	nitrile	DiBAH	THF	61%	J. Med. Chem. 34,9 (1991) 2922-2925
	10	2	primary amide	LiAlH(NEt ₂) ₃	room temp. 12 hrs	53%	THL 32,41 (1991) 6903-6904
	11	2	N-methoxy-N-methylamide	DiBAH	THF -100°C	51%	Heterocycles 53 (2000) 2183-2190

It can be seen from the review that the known methods either require expensive reagents (Example Nos. 1, 3, 10), use raw materials which are not available in industrial quantities (Example Nos. 1, 3, 11), can only be carried out with the nitrile, which is itself prepared in three steps (Example 5 Nos. 2, 3, 4, 7, 9) or require low temperatures (Example Nos. 2, 4, 11). From the point of view of the yield, only Example Nos. 1, 2 and 3 are economically viable. If the reagent costs are taken into account, only the process of Example No. 2 remains. However, the latter requires three reaction 10 steps starting from nicotinic acid and relies on the maintenance of low temperatures.

Surprisingly, the inventors of the present patent application have now found that nicotinaldehydes can be obtained in virtually quantitative yields by reduction under standard conditions (room temperature, atmospheric 15 pressure) if the starting materials employed are the corresponding morpholinamides. Morpholinamides of nicotinic acid and derivatives thereof were previously unknown as aldehyde precursors.

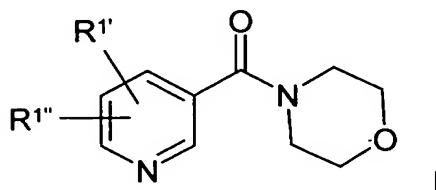
20 The present invention thus relates to a process for the preparation of nicotinaldehydes, characterised in that the starting materials employed for the reduction are the corresponding morpholinamides. The said process is preferably carried out at room temperature and without pressure (under atmospheric pressure).

25 Reducing agents which are preferred in accordance with the invention here are lithium alkoxyaluminium hydrides containing one to three alkoxy radicals. The general formula is $\text{LiAlH}_{(4-n)}(\text{OR})_n$, where n can be = 1, 2 or 3. Suitable radicals are straight-chain or branched aliphatics, such as, for 30 example, methyl, ethyl and tert-butyl. The reduction succeeds particularly selectively with $\text{LiAlH}(\text{OEt})_3$. Likewise suitable as reducing agent for the

preparation process according to the invention is the considerably cheaper $\text{LiAlH}_3(\text{OEt})$.

In a preferred embodiment, nicotinic acid morpholinamides of the formula I

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I

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in which

R^1 , $\text{R}^{1''}$ each, independently of one another, denotes H, Hal, A, OA, CH_2R^2 or Ar,

R^2 denotes OA or NA_2 ,

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A denotes unbranched or branched alkyl having 1-10 C atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by $-\text{CH}=\text{CH}-$ groups and/or also 1-7 H atoms may be replaced by F,

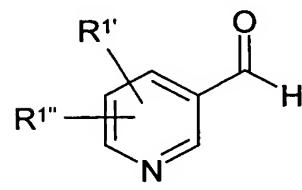
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Ar denotes an unsaturated, partially or fully saturated, mono- or polycyclic homo- or heterocyclic system with the hetero atoms O, N, S which is unsubstituted or mono- or polysubstituted by Hal, A, OA, NA_2 , NO_2 , NASO_2A , SO_2NA , SO_2A , and

Hal denotes F, Cl, Br or I,

as starting materials are reduced to nicotinaldehydes of the formula II

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II

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The above-mentioned radicals preferably have the following meanings here:

R^1 , $R^{1''}$ each, independently of one another, denotes H, Hal, A, OA, CH_2R^2 or Ar, where A, Ar, Hal and R^2 have one of the meanings described below.

R^1 , $R^{1''}$ are, in particular, hydrogen, methoxy, ethoxy, propoxy, butoxy, fluorine, chlorine, bromine, iodine, phenyl or o, m or p-substituted phenyl. R^1 is particularly preferably p-fluorophenyl or bromine and $R^{1''}$ is simultaneously hydrogen.

Hal denotes fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine.

R^2 denotes OA or NA_2 , where A has the meaning indicated above and below.

A denotes alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms.

A preferably denotes methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl.

A very particularly preferably denotes alkyl having 1-6 C atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, trifluoromethyl, pentafluoroethyl or 1,1,1-trifluoroethyl.

Furthermore, A denotes cycloalkyl, preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or 2,6,6-trimethylbicyclo-[3.1.1]heptyl, but likewise mono- or bicyclic terpenes, preferably p-menthane, menthol, pinane, bornane or camphor, where each known stereoisomeric form is included, or adamantyl. For camphor, this denotes both L-camphor and D-camphor.

Ar denotes an unsaturated, partially or fully saturated, mono- or polycyclic homo- or heterocyclic system with the hetero atoms O, N, S which is unsubstituted or mono- or polysubstituted by Hal, A, OA, NA₂, NO₂, NASO₂A, SO₂NA₂, SO₂A.

5 Preferred cyclic systems are unsubstituted or substituted phenyl, naphthyl or biphenyl, specifically preferably phenyl, o-, m- or p-tolyl, o-, m- or p-cyanophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-di-
10 chlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl.

Particularly preferred starting materials for the aldehyde synthesis according to the invention are 5-(4-fluorophenyl)nicotinic acid morpholinamide and
15 5-bromonicotinic acid morpholinamide.

The present invention accordingly also relates to the use of nicotinic acid morpholinamides, preferably 5-(4-fluorophenyl)nicotinic acid morpholinamide or 5-bromonicotinic acid morpholinamide, for the preparation of the
20 corresponding nicotinaldehydes.

The present invention furthermore relates to 5-(4-fluorophenyl)nicotinic acid morpholinamide and 5-bromonicotinic acid morpholinamide as starting materials in the synthesis according to the invention.

25 The reaction according to the invention is generally carried out in an inert solvent. Examples of suitable inert solvents for the reactions described above are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol dimethyl ether (diglyme); or mixtures of the said solvents. Particular preference is given to ethers, in particular tetrahydrofuran.

The amount of solvent is not crucial, in general 5 g to 500 g, preferably 10 g to 100 g of solvent can be added per g of starting material.

The reaction temperature for the reactions described above is, depending on the conditions used, between about -10° and 200°, normally between -10° and 100°, in particular between 0° and 50°, but preferably 10° to 40°, particularly preferably room temperature.

The reaction time is, depending on the conditions used, between a few seconds and several hours, preferably between 1 minute and 3 hours.

However, the reaction according to the invention will very generally be complete after 0.1 to 1.5 hours.

For the purposes of this invention, the "conditions used" is taken to mean the substitution pattern of the nicotinic acid morpholinamide, the type and amount of the solvent, the type and amount of the reducing agent, the reaction duration, the reaction temperature and further details of the performance of the reaction, such as, for example, the stirrer speed or the other nature of the reaction vessel.

In general, the end of the reduction according to the invention to the aldehyde is determined by suitable analytical methods, for example thin-layer chromatography or HPLC, and the reduction is terminated.

The nicotinaldehydes according to the invention can be obtained after removal of the solvent by conventional work-up steps, such as, for example, addition of water or acid to the reaction mixture and extraction. It may be advantageous subsequently to carry out a distillation or crystallisation for further purification of the product.

The nicotinic acid morpholinamides used as starting materials for the process according to the invention can be prepared by methods known per se, as described in the literature (for example in standard works, such as

Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. However, use can also be made of variants known per se which are not mentioned here in greater detail.

5 In general, the following procedure is followed:

The nicotinic acid is converted, using a suitable reagent, such as, for example, thionyl chloride, into the acid chloride, which is subsequently 10 reacted with the desired amine to give the amide.

In order to protect substituents against undesired reactions during the reduction according to the invention and/or subsequent work-up steps, protecting groups are employed where appropriate and removed again 15 after reduction of the nicotinic acid morpholinamide. Methods for the use of protecting groups are described, for example, in Theodora W. Green, Peter G. M. Wuts: Protective Groups in Organic Synthesis, 3rd Edition John Wiley & Sons (1999).

20 Even without further embodiments, it is assumed that a person skilled in the art will be able to utilise the above description in the broadest scope. The preferred embodiments should therefore merely be regarded as descriptive disclosure which is absolutely not limiting in any way.

25 **Example 1: Preparation of 5-(4-fluorophenyl)nicotinaldehyde from 5-(4-fluorophenyl)pyridine-3-carboxylic acid morpholinamide**

(a) Synthesis of the precursor 5-(4-fluorophenyl)pyridine-3-carboxylic acid

30 Firstly, 5-(4-fluorophenyl)pyridine-3-carboxylic acid is prepared by Suzuki coupling (N. Miyaura, A. Suzuki, Chem. Rev. 95, 2457 (1995)) by reacting

5-bromonicotinic acid with p-fluorobenzeneboronic acid (both commercially available) under reaction conditions known per se to give 5-(4-fluorophenyl)pyridine-3-carboxylic acid.

5 (b1) Synthesis of 5-(4-fluorophenyl)pyridine-3-carboxylic acid morpholinamide – Variant 1

25.6 g of 5-(4-fluorophenyl)nicotinic acid are initially introduced in 200 ml of toluene, and 25.1 g of thionyl chloride are then added at room temperature. The mixture is then warmed at 90°C for 18 hours, and the unreacted thionyl 10 chloride and some of the solvent are subsequently distilled off. After the distilled-off volume has been made up with toluene, 12.4 g of morpholine are added at 80 to 100°C, and the reaction mixture is cooled after 2 hours. pH 8 is set by addition of sodium hydroxide solution, and the product is separated off by extraction with toluene. After decolourisation using 15 activated carbon and removal of the solvent by distillation, 27.7 g of 5-(4-fluorophenyl)pyridine-3-carboxylic acid morpholinamide remain as solid (melting point: 100-102°C, yield: 81% of theory)

20 (b2) Synthesis of 5-(4-fluorophenyl)pyridine-3-carboxylic acid morpholinamide – Variant 2

1.2 g of Pd[P(Ph)₃]₄ and 7.6 g of p-fluorobenzeneboronic acid are added to a solution of 14.3 g of 5-bromonicotinic acid morpholinamide in 100 g of THF. A solution of 8.0 g of Na₂CO₃ in 25 g of water is subsequently added dropwise with stirring at 65°C. After 16 hours, the reaction mixture is cooled 25 and evaporated in a rotary evaporator. The residue is taken up in dichloromethane, activated carbon is added, and the mixture is filtered. Repeated extraction of the filtrate with water and evaporation in a rotary evaporator gives a residue of 15.7 g, which, according to HPLC, comprises 89% of 5-(4-fluorophenyl)pyridine-3-carboxylic acid morpholinamide (net 30 yield 93% of theory). Recrystallisation from ethyl acetate gives 8.0 g of 5-(4-fluorophenyl)pyridine-3-carboxylic acid morpholinamide having an HPLC purity of 99.6% (53.3% of theory).

(c) Preparation of 5-(4-fluorophenyl)nicotinaldehyde

6.0 g of 5-(4-fluorophenyl)pyridine-3-carboxylic acid morpholinamide from Example 1(b) are dissolved in 30 ml of THF, and 57 g of a 13.6% LiAlH-
5 (OEt)₃ solution in THF are added over the course of 10 minutes at 30°C to 35°C. After 1 hour, 30 ml of 12.5% sulfuric acid are added, and the organic phase is separated off. The aqueous phase is adjusted to pH 1 using sulfuric acid and extracted a number of times with methyl tert-butyl ether. The organic phases are then combined, extracted once with water and then
10 evaporated, leaving a residue of 4.3 g having a content of 97% by weight of 5-(4-fluorophenyl)pyridine-3-carbaldehyde (yield = 98% of theory).

**Example 2 (comparative example to Example 1, use of the piperidin-amide instead of the morpholinamide): Preparation of 5-(4-fluorophenyl)-
15 nicotinaldehyde from 5-(4-fluorophenyl)pyridine-3-carboxylic acid piperidinamide**

36.7 g of 10% LiAlH₄ solution are diluted with 75 g of THF, and a mixture of 8.88 g of ethyl acetate and 75 g of THF is then added at 0°C. At -7°C, a
20 solution of 6.8 g of 5-(4-fluorophenyl)pyridine-3-carboxylic acid piperidin-amide in 24.7 ml of THF is added. After three hours, the mixture is added to 190 g of 10% sulfuric acid. The pH is adjusted to 3 using sodium hydroxide solution, and the THF is then substantially removed by distillation. Extraction with methyl tert-butyl ether and evaporation leaves 2.6 g of solid
25 (content according to HPLC 67 area-%, corresp. to 36% of theory)

Example 3: Preparation of 5-bromonicotinaldehyde from 5-bromopyridine-3-carboxylic acid morpholinamide

30 (a) Synthesis of 5-bromopyridine-3-carboxylic acid morpholinamide

50.4 g of 5-bromonicotinic acid and 87.5 g of morpholine are heated to reflux in 200 ml of xylene, and the water formed is distilled off. After cooling, the reaction mixture is extracted three times with 10% sodium hydroxide solution and then twice with water. After the xylene has been distilled
5 off, the residue is recrystallised from ethyl acetate. The yield after drying is 19.2 g (28.3% of theory). Melting point 80°C.

(b) Preparation of 5-bromonicotinaldehyde

10 1.75 g of lithium aluminium hydride powder are suspended in 64 g of THF. A mixture of 5.9 g of ethyl acetate and 28 g of THF is subsequently added dropwise with cooling. After 30 minutes, this reaction mixture is added dropwise at 0°C to 10°C to a solution of 5.0 g of 5-bromopyridine-3-carboxylic acid morpholinamide from Example 3(a) in 30 g of THF (this corresponds to 150% excess of the reducing agent). After 1 hour, the reaction
15 mixture is poured into 35 ml of 12% sulfuric acid, and the organic phase is evaporated to dryness. Recrystallisation from MTB ether and drying gives 1.91 g of product (= 55.7% of theory). Melting point 95°C.

20 As can be seen from comparison of the respective reaction yields of Examples 1 and 2, the use of the nicotinic acid piperidinamide, an alternative nicotinamide – but one which is closely structurally related to the morpholinamide – results in a significantly worse reaction.

25 By contrast, a better yield can be achieved on use of the morpholinamide, even with a large excess of the reducing agent (Example 3) than in the case of correct stoichiometry in Example 2, in which piperidine is used as amine component.